

## REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 1-20, 27-43, 46-47, 52-55, and 58-61 are pending. Claims 9-10 and 14-20 stand withdrawn from consideration as allegedly drawn to a non-elected species. Claim 5 has been amended to more specifically define the claimed subject matter. No new matter has been added.

### Rejection under 35 U.S.C. § 102(b)

Claims 1-3, 5-7 and 35 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ruoslahti *et al.* (U.S. Pat. No. 5,627,263, 1997) in the Office Action dated June 30, 2000. However, the above reference was indicated as incorrectly cited in the Advisory Action dated July 2, 2001. The Advisory Action further states that the above claims now stand rejected under 35 U.S.C. § 102(e) as being anticipated by another U.S. patent to Ruoslahti *et al.* (*i.e.*, U.S. Patent No. 5,981,478), instead. In particular, the Advisory Action states that Ruoslahti *et al.* teach the sequence CRGDFVGC (citing Table 3 of the referenced patent), comprising at least 5 and 7 consecutive amino acids of SEQ ID NO:1.

Applicants respectfully traverse this ground of rejection. Claims 3 and 4 recite that Aaa is not glycine when Lys/Arg is arginine and Baa is aspartic acid. Such recitation excludes the sequence CRGDFVGC disclosed by Ruoslahti *et al.* Accordingly, amended claims 3 and 4, as well as dependent claims thereof, are not anticipated by Ruoslahti *et al.*

Claims 2, 35 and 40 stand rejected under 35 U.S.C. § 102(b) as anticipated by Bult *et al.* (Science 273: 1058-73, 1996). In particular, the final Office Action asserts that Bult *et al.* teach a 47mer protein that comprises the sequence IYSYX and that a Genbank submission by Kohara (GenBank Acc. No. D64402, 1995) indicates that the genomic sequence is correct and functions in an open reading frame. In responding to Applicants' remarks that the nucleotide sequence of the submission does not contain the information as to its reading frame, the Advisory Action insists that the Genbank submission does indicate the reading frame.

Applicants respectfully traverse this ground of rejection. The Bult reference merely describes the entire genomic sequence of the prokaryotic organism *Methanococcus jannaschii* and depicts many predicted open reading frames. Some of these open reading frames have been predicted to be related to certain known proteins while others have not. The specific sequence cited by the Action is defined by no more than a number (*i.e.*, MJ0802). Further, there is no indication that the sequence is correct or that it is actually a functional open reading frame. The above deficiencies have not been remedied by the Genbank submission. This submission is an mRNA sequence of the eukaryotic organism *Caenorhabditis elegans* and cannot prove that the genomic sequence of the different, prokaryotic organism *M. jannaschii* is correct and functions in an open reading frame. In addition, this submission, at most, indicates that the nucleotide sequence is expressed in *C. elegans* and may be translated in one or more of the six possible reading frames. It does not, however, indicate to one of ordinary skill in the art in which particular reading frame(s) the nucleotide sequence is translated. Should this ground of rejection be maintained, an explanation of why one of ordinary skill in the art would know the particular reading frame(s) is respectfully requested.

Accordingly, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection under 35 U.S.C. § 102(b) is respectfully requested.

#### Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-4, 5-8, 11-13, 27-43, 46-49, 52-55 and 58-61 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled. In particular, the Action asserts that the specification is not enabling for the current claim scope because it does not disclose the sequence identity of cell adhesion recognition (CAR)-containing peptides that actually reduce cell adhesion in the disclosed example, nor the 9 amino acid CAR sequence used to make the antibodies that have cell adhesion modulating activity as disclosed in Examples 2 and 4. Accordingly, the Action concludes that there is no clear guidance that an agent comprising SEQ ID NO:1 is capable of modulating claudin-mediated processes, such as cell adhesion. The Action further asserts that there is no predictability that the CAR sequence (based on an alignment with other mammalian claudins) would confer the biological activities such as cell adhesion to an agent comprising the CAR sequence because the specification does not disclose

where the biological activity of cell adhesion of the claudin resides within SEQ ID NO:1 and if this consensus sequence alone is sufficient.

Applicants respectfully traverse this ground of rejection. Briefly, with respect to enablement, nothing more than objective enablement is required in order to meet the requirements of 35 U.S.C. § 112, first paragraph. In particular, as stated by the Board of Patent Appeals and Interferences:

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *Staehelin v. Secher*, 24 USPQ 2d 1513, 1516 (B.P.A.I. 1992) (citing *In re Marzocchi* 169 USPQ 367, 369 (C.C.P.A. 1971)) (emphasis original).

In the instant case, the reasonable basis that the specification lacks enablement has not been established in the Action. No evidentiary support is provided in the Action to indicate that one of ordinary skill in the art would doubt the cell adhesion modulating activities of the claimed agents. Should this ground of rejection maintained, such evidentiary support is respectfully requested.

Applicants respectfully submit that the identification of SEQ ID NO:1 based on alignment studies of various claudin sequences does not cast doubt on the enablement of the present application. As one of ordinary skill in the art would appreciate, the portion of a protein important for, or essential to, the function of the protein is usually highly conserved through evolution. Thus, that person would not doubt the possibility that an agent comprising the conserved amino acid residues in the important or essential portion of the protein retains the function of the protein or affects the interaction between the protein molecules themselves or between the protein and another protein. Likewise, in the instant case, one skilled in the art would not doubt the possibility that an agent comprising SEQ ID NO:1, a consensus sequence based on alignment studies, retains claudin's function and/or affects the interaction between a claudin molecule and another molecule.

To further address the skepticism of the Action as to the cell adhesion modulating activities of the claimed agents that comprises SEQ ID NO:1 or portions thereof, Applicants herein enclose an example (*i.e.*, Example 5), as well as two figures that the example refers to (*i.e.*, Figures 3 and 4), in a related application (*i.e.*, U.S. Pat. App. No. 09/434,355) that indicate that a peptide comprising SEQ ID NO:1 (*i.e.*, N-Ac-WKIYSYAGDN-NH<sub>2</sub>) is capable of inhibiting the formation of tight junctions in epithelial cells. This example shows that a specific embodiment of the claimed invention has the cell adhesion modulating activity.

In addition, the specification also discloses various assays to determine cell adhesion modulating activities of a particular agent (*see, e.g.*, page 39, line 27 to page 45, line 11). In view of the teaching of the present application, one of ordinary skill in the art would be able to determine whether a given agent comprising SEQ ID NO:1 or a portion thereof has the ability of modulating cell adhesion through routine experimentation.

Accordingly, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 2-8, 11-13, 27-43, 46-49, 52-55 and 58-61 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not adequately described in the specification. More specifically, the Action claims that even if the consensus sequence is adequately described, the specification does not provide adequate description of a claudin CAR sequence, specifically, what sets apart claudin sequences as a genus from those that are not claudin sequences.

Applicants respectfully traverse this ground of rejection. Applicants believe that the present specification provides adequate description of claudin sequences, and that in view of such description, one of ordinary skill in the art would be able to distinguish claudin sequences from those that are not. For instance, the specification defines the term “claudin as an integral membrane protein with a molecular weight of approximately 22 KD, which contains two extracellular domains and four transmembrane domains (as determined by hydrophobicity analysis) and which displays at least 30% sequence identity to a member of the claudin family specifically recited in the present application” (*see, e.g.*, page 16, lines 12 to 16). The

specification further provides exemplary members of the claudin family, including claudin-1, claudin-2, CPE-R and RVP-1 (*see, e.g.*, page 16, lines 16-24 and Figure 1). In addition, a claudin molecule also contains a claudin CAR sequence exemplified by the consensus sequence of SEQ ID NO:1 (*see, e.g.*, page 16, lines 10-12); is capable of homophilic or heterophilic interactions (*see, e.g.*, page 3, lines 16-19); and is a component of tight junction (*see, e.g.*, page 3, lines 6-7). Using the above criteria, one of ordinary skill in the art would readily know whether a particular sequence is a member of the claudin family.

Accordingly, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

#### Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite. More specifically, the Action states that the recitation of an agent comprising a peptide ranging in size from 3 to 50 amino acid residues is indefinite, since claims 2-4 on which claim 5 depends encompass at least 5, 7, and 8 consecutive amino acid residues of SEQ ID NO:1, respectively.

Applicants thank the Examiner for noting this informality and amend claim 5 to recite that the size of the peptide is from 5 to 50 amino acid residues. Accordingly, Applicants respectfully submit that this ground of rejection has been overcome and request its withdrawal.

#### Rejection under 35 U.S.C. § 112, First Paragraph (New Matter)

Claims 2-3, 5-8, 11-13, 27-43, 46-49, 52-55 and 58-61 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. More specifically, the Examiner asserts that there is no support in the specification or claims as originally filed for the recitation "wherein Aaa is not glycine when Lys/Arg is arginine and Baa is aspartic acid."

Applicants respectfully traverse this ground of rejection. Applicants submit that the above recitation is sufficiently supported by the present specification and thus does not constitute new matter. The originally claimed modulating agents are described throughout the

application (*see, e.g.*, page 4, line 15 to page 10, line 10; and page 14, line 24 to page 38, line 18). Such modulating agents inherently include those where Aaa is any amino acid other than glycine when Lys/Arg is arginine and Baa is aspartic acid, as well as those where Aaa is glycine when Lys/Arg is arginine and Baa is aspartic acid. The amendment to claims 2 and 3 is merely to exclude the latter subgroup. Because the remaining former subgroup is inherently disclosed in the present application, claims directed to this subgroup are sufficiently supported.

The instant case is analogous to the situation in *In re Johnson* (194 USPQ 187 (CCPA 1977)), where the Applicants, in a continuation-in-part (CIP) application, claimed a genus minus two species already disclosed by others and the priority date of the grandparent application that disclosed the genus. The Board of Appeals held that the claims in the CIP application were not entitled to the priority date of the grandparent application because the grandparent application did not provide sufficient support for the later claimed genus minus two species. The court disagreed and held that the grandparent application provided sufficient support for the claims in the CIP application and thus provided the priority date for the subsequent CIP application. The court stated that because inventions are constantly made which turn out not to be patentable and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable, it is for the inventor to decide what bounds of protection he will seek. *Id.*, at 194-195 (citing *In re Saunders*, 170 USPQ 213, 220 (1971)). The court further stated: "To deny appellants the benefit of their grandparent application in this case would . . . let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed." *Id.*, at 195. Accordingly, Applicants respectfully submit that a negative limitation is appropriate and thus request withdrawal of the rejection.

Applicants note that the Information Disclosure Statement filed on February 25, 1999 has not been acknowledged by the Examiner. Accordingly, Applicants respectfully request that the IDS be entered and the references be acknowledged.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings**

to Show Changes Made.” Also enclosed is a copy of Limited Recognition Under 35 CFR § 10.9(b).

Applicants respectfully submit that all claims in the application are in condition for allowance and request that the Examiner issue a Notice to that effect. If any issues remain with regard to patentability, the Examiner is invited to telephone the undersigned at (206) 622-4900 to resolve these issues and place this application in condition for allowance.

Respectfully submitted,

Orest W. Blaschuk et al.

Seed Intellectual Property Law Group PLLC



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Qing Lin, Ph.D.

(See Limited Recognition)

QXL:jab

Enclosures:

- Postcard
- Check
- Request for CPA (+ copy)
- Version With Markings to Show Changes Made
- Exhibit 1: Example 5
- Exhibit 2: Figure 3
- Exhibit 3: Figure 4
- Petition for an Extension of Time
- Copy of Limited Recognition Under 35 CFR § 10.9(b).

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 5 has been amended as follows:

5. (Twice Amended) A modulating agent according to any one of claims 2-4, wherein the agent is a peptide ranging in size from 53 to 50 amino acid residues.

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## EXAMPLE 5

Effect of Representative Modulating Agents on  
Electrical Resistance Across Cell Monolayer

This Example illustrates an electrical resistance assay for evaluating the effects of claudin-modulating agents on epithelial cell adhesion.

Madin Darby canine kidney (MDCK) cells were plated in Millicells (Millipore, Bedford, MA), at a density of 300,000 cells per Millicell, and cultured in Dulbecco's Modified Eagle Medium (DMEM; Sigma, St. Louis, MO) containing 5% fetal calf serum (Sigma, St. Louis, MO) until monolayers formed. Monolayers were exposed to the modulating agent dissolved in medium. The electrical resistance was measured using the EVOM device (World Precision Instruments, Sarasota, FL). At the time of measurement, fresh medium, with or without the modulating agent, may be added to the Millicells.

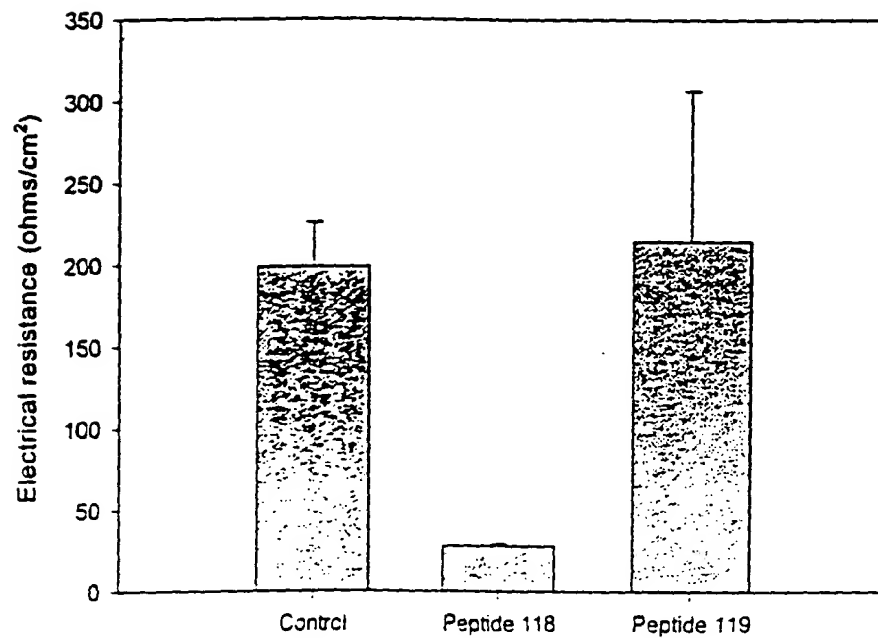
Figure 3 shows the mean electrical resistance across MDCK cell monolayers cultured for 18 hours in medium alone (Control), medium containing N-Ac-WKIYSYAGDN-NH<sub>2</sub> (Peptide 118; SEQ ID NO:475) or H-WKIYSYAGDN-NH<sub>2</sub> (Peptide 119; SEQ ID NO:475) at a concentration of 0.5 mg/ml. Duplicate measurements were taken, and error bars represent the standard deviation. Peptide 118 reduced the electrical resistance across the monolayer, while peptide 119 did not change the electrical resistance across the monolayer relative to the control.

Figure 4 shows the mean electrical resistance across MDCK cell monolayers cultured for 24 hours in medium alone (Control) or medium containing N-Ac-WKIYSYAGDN-NH<sub>2</sub> (Peptide 118; SEQ ID NO:475) at various concentrations. Peptide 118 reduced the electrical resistance across the monolayer in a dose dependent manner.

These results demonstrate the ability of modulating agents to inhibit the formation of tight junctions in epithelial cells, as well as the effect of the N-Ac group of activity of this particular modulating agent.

From the foregoing, it will be evident that although specific embodiments of the invention have been described herein for the purpose of illustrating the invention, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

Effect of claudin CAR sequence peptides at 0.5 mg/ml on  
electrical resistance of MDCK monolayers after 18 hours



**Effect of claudin CAR sequence peptides at various concentrations on electrical resistance on MDCK monolayers after 24 hours**

